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From Gender to Genomics: Achievements and Challenges in Sex-Specific Science

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From Gender to Genomics: Achievements and Challenges in Sex-Specific Science*

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What I would like to talk about today is an overview, of sorts, of what I have gleaned in my long saga of trying to understand about the differences between the sexes, at all levels, and whether or not they are important to us who are practicing physicians. As heard as a subtext today, scientific research and medical practice come from the societies in which they are imbedded. We do not spring antiseptically prepared and fully formed as objective characters from the brow of Zeus. We reflect our own history, our own perceptions, and it is not surprising that as Heraclitus said, "Nothing is constant but change." And we change opinions and views as the society around us does.

The past two decades have been really interesting, because of the profundity of the change and how we approach biomedical investigation in terms of whom we look at and what we are looking for. We have what could really be called a radically new view of normal biology and the pathophysiology of disease. I was thinking this morning, listening to the experts on coronary disease, that the impact of estrogen on nitrous oxide in the endothelium of women was not even mentioned and so, our knowledge far exceeds the time that we are given to talk, but there are some very interesting dilemmas and little byways in the differences in the pathogenesis of coronary disease between the sexes that are fascinating and here is why.

Up until the 1980s, we had what I called the bikini view of medicine. Men were considered normative for the whole population, and paradoxically I think we have exploited men and not really considered the things that are unique to them in terms of vulnerability and their needs. My

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last book is called *Why Men Die First.* And although the title is somewhat prohibitive—men don't pick it up in my office—it is a very interesting treatise on the fact that while we have done all of our biological or biomedical research on males for very interesting reasons, most of them very practical, we have not really considered their unique needs.

The other eternal question, which was formed as we began to study women and noticed the variety and extent of the differences between men and women in all the systems of the body, is what about a man or a woman is hard-wired in terms of the biology, inescapable and immutable, and which are the consequences of training, social forces, and the environment? We will never really get the answers to that question but it is *the* question that I think should be in all of our minds as we look at the differences between the sexes.

Progress and medicine, like everything, is embedded in history and I want to show you what I think the elements were and how women came to insist upon and receive attention from the biomedical community.

First, women in 1900 had very little control over the world around them and their best bet for power over the environment was marriage or an alliance with a powerful man. The average life expectancy was forty-eight for both sexes, so the whole question of menopause and aging only arose almost peripherally. Finally, the third ingredient in the last century was that the physician had very little power over disease in terms of cure or prevention. His best efforts were—and this can be seen in any text from that time—in the brilliant description of disease and its course. He was a great prophet of what would happen to the patient he was observing and so he was invested with sort of magical powers and a seeing eye that none of the rest of the public had. That was the situation.

World War II, and a little bit less impressively World War I, was tremendously significant in the history of why we are now so interested in women. First of all, men were away long enough, and in enough numbers, so that women had to fulfill roles that they had never filled before. Dr. Irene Ferrer was appointed the first Chief Resident of Medicine at Columbia University at the Bellevue site, simply because there were no men to take that place. The second thing is that the exigencies of the war forced scientists and particularly physicians to develop capacities they never before had the need to develop. For example, the whole discipline of plastic surgery began on the battle fields of World War I when John Converse, as a twenty-three-year-old surgeon with one year of training saw the ravages of the wounds that the French army was experiencing and he began to develop what was a rather well-developed system of plastic repair. Finally, you might like to know that the third-party payer came into existence for the first time during World War II. A historical idea, because wages and prices were frozen, the Kaiser shipping company decided that it would give health care plans to its employees and it was used to develop

the notion that a corporation, and by analogy, a government, was responsible for the health of its people. It was a revolutionary concept at the time.

So these were the huge changes of World War II. And the rise of feminism that was inevitable after World War II, when women would not go back to the kitchens and other kinds of domestic pursuits, but had a sense of their competence and their ability to make decisions that they did not relinquish. That, and the tremendous belief of the American public in the omnipotence of science and the importance of scientific achievement as we emerge from World War II, opened the way to a new era in medical investigation.

In 1944, the American Congress passed an act, the Public Health Service Act, which tremendously increased the amount of money that the taxpayer would devote to science. An associate professor from NYU, James Shannon, was sent down to the National Institutes of Health (NIH), which at the time consisted of four little wooden buildings in Bethesda, and he presided in the next thirteen years over a tremendous expansion in resources—both human and brick and mortar—at the NIH. It made the NIH, by the mid-1960s, the foremost leader in biomedical technology and knowledge, and started what is arguably the jewel in the crown of the United States.

The decades that followed the war were very much colored by the Nuremberg Trials and the discovery of the atrocities that had been perpetrated on unwilling subjects, without their consent or knowledge. This spawned a whole sequence of protective legislation in this country and others, which really concentrated on the rights of the individual to understand what research was being proposed, the risks involved, and a development of safeguards for the subject. The Kefauver Harris Amendments were prompted by the thalidomide disaster and it gave meat-and-bones, so to speak, to the FDA for the first time. The Helsinki Declaration reiterated the rights of the patient to refuse and/or participate in clinical investigations, which sprang out of the atrocities that came out from Nuremberg. We had the National Research Act of 1974 and finally, and this was a turning point, the Belmont Report, which for the first time said that if women were to benefit from the consequences of medical investigation, that they had in justice an obligation to participate in the risk of clinical investigation, an idea that had not really been advanced before.

So, women's health came into its own and so did women's risks. Really, they entered a new era, from 1985 to 1999, also supported by legislation, both at the congressional level, at the NIH, and in part from the FDA, so that by the end of the century, we understood that women were important to study, that they had tremendous and widespread differences from men, and that, when we compared the data from men and women, we formulated questions we never would otherwise have asked. This

transformative decade at the end of the century has really been a turning point for us. The medical investigation literature began to be apparent in the 1990s in the cardiovascular community.

In 1988 we began a substantive movement to directly investigate women. By 1994 and through 2000, we formulated the idea that the study of both male and females, in spite of our wish to protect women and to have "a standardized system," namely the male, in which to do investigation, was flawed. We developed the notion of gender-specific medicine all throughout this country, and Florence Haseltine is one of my most admired forerunners of the notion that women's health is important. She was one of the people that helped couch it in terms of the relevance to men's health as well. The other great door that opened was the description of the human genome in 2000, and the Encode, which is an international society that continues to explain how complex the regulation of the genome is and how many factors enter into it, came into being.

So where are we now in the first decade of this century? We are more aware than we have ever been in human history of the extent and complexity of sex and gender-specific properties of living organisms. We are exploring, as a second point, a very interesting interface between the environment, our genome, and the phenotype. We are what we experience, in a very real sense, and there is no such thing as "hardwired" that's independent of the environment in which we and all living things are raised.

Finally, we have the latest challenge in medicine that I would like to talk to you about: synthetic biology. There is a new age, coming or here, headed by Craig Venter, George Church at MIT, and others. It is the age of synthetic biology and for the first time in history, arguably, it can be said that we have the power to generate entirely new forms of life in quite simple ways, in many respects, which themselves may be capable of reproductions. This is a new power that we have.

So, here are some important issues. No matter how often we ask the question and debate it as we used to at the NIH, at the Office of Research on Women's Health, we will never answer the question about how hard-wired and immutable our lives are. Some people say we do not even have free will because of our biological constitutions. What is the impact of other factors, what can we do with training, education, social reforms, and so on, to impact the phenotype and the way that people behave? The second important question is, does sex matter? Can we just take a cheek swab and send it off to someplace and find out what's going to happen to us, what we are susceptible to? Does whether we are male or female have an impact on the expression of our DNA? I had the enviable opportunity as a second of a keynote address in Tel Aviv to follow a Nobel Laureate, who said gender was out, that it did not matter anymore, that male and female did not matter, all that we had to do was look at the genome and we get the

answers. In fact, the same genes are expressed differently depending upon the sex of the individual. The take-home message is that it is not possible, in my opinion, to separate the organism from its experience, and to answer what is sex-specific, and what is gender-specific. It is not a question anymore, it all follows a final common path, and how we are treated has an important consequence to what we inevitably become. And this quote is worth reading: "[t]here is no gene-controlled inheritable trait that cannot be altered by the environment. [. . .] Humans enter the world as a work-in-progress [. . .] nature/nurture is not an *either/or* duality, but, rather represents a *both/and* type of complementarity."[1] It is not a duality. So all of you, each one of you, is what you have in your DNA, but also where you have been, and what you have learned from the world in which you were placed.

A new dawn certainly came to the world in 2000, when the White House announced a completion of a rough draft of the genome, and three years later, the Human Genome Project announced a much more complete and accurate version. Now we understood that there was a pattern, how it worked. Marshall Nuremberg was a great friend of mine, and the description of how he explained the code, how he broke the code of the human genome, was one of the most poignant and beautiful experiences and conversations I have ever had. He was about thirty-five years old as I recall, very young.

To say that the genome is the Rosetta Stone for disease, and that we can take your DNA and tell you what is going to happen to you, is absurd because it ignores the impact of the things I have been talking about: the physical, chemical, and environmental factors. We don't want to be reductionist or simplistic. As I have said in fifty ways up until now, the whole regulation of how your genes are expressed is incredibly complex, and the complexity continues to evolve in ways that stagger my mind as I read about it. We want to know what the organizational nature of the whole organism is, not just its disparate parts, so we have to look at things, as it were, in context.

Three hundred million years ago there were no males and females and then there was a mutation on one of the X-chromosomes that made it an isolationist gene in a way, which I like to think tells us something about men and their nature. The chromosome could not combine any longer with X, look to it for repairs or exchanges along most of its length. And it also became the determinate of male sex. That's how we got it, but the important questions are how do the sexes differ, which is heartier and in

1. LEONARD SHLAIN, SEX, TIME AND POWER: HOW WOMEN'S SEXUALITY SHAPED HUMAN EVOLUTION xvi (2003).

what respect, and how is the prevention and cure of disease different as a function of whether our patient is male or female.

Now, maleness and femaleness is not just a question of gonadal hormones. How many of you have heard of this remarkable bird that is half male and half female? This bird alighted in the prepared environment of an investigator, and the bird had a testicle, a testes, on one side of its body, male plumage, and a male configuration to its brain. And on the other side, an ovary, a female brain, and female plumage. So here was this hermaphroditic organism that appeared quite frequently actually in nature, bathed by the same hormones, but clearly had a sexually dimorphic brain. The song that was generated depended upon the abilities of the male brain to generate the characteristic mating call of the finch; the female part of the brain was unable to do this. I found that really fascinating, but it was, in fact, this model, a natural proof that hormones don't determine our destiny either.

There was a spectacular paper by Yang's group, from California, which showed that thousands of genes are expressed differently in at least four tissues of the body depending on whether the owner of that same gene is male or female.[2] That's amazing, we had no idea. As Yang's group said, "We saw striking and measurable differences in more than half of the genes' expression patterns between males and females. We didn't expect that."[3] Echoing the words of the Institute of Medicine's first monograph on sex, entitled in part "Does Sex Matter?," the editor wrote, "Sex does matter. It matters in ways that we did not expect. Undoubtedly, it also matters in ways that we have not begun to imagine."[4]

So this has all come as a great surprise. Sex is important. Men and women are different. We are all products, in part, of our biologic wiring if you will, but also, importantly, as a result of how we are treated and trained.

Is manipulating the genome, which we are clearly doing, and certainly more and more extensively planning to do, interfering with evolution, or by definition, is it a continuation of evolution and our capacities to overcome challenge and change the world in which we live? Scientists are taking genes out and inserting others. They are creating biologic specimens capable of reproduction. And they are giving us an increasingly precise

2. *See* Xia Yang et al., *Tissue-Specific Expression and Regulation of Sexually Dimorphic Genes in Mice*, 16 GENOME RES. 995 (2006).

3. News Release, Elaine Schmidt, Health Sciences Media Relations, UCLA, UCLA Study Finds Same Genes Act Differently in Males and Females; Discovery May Explain Gender Gap in Disease Risk, Drug Response (July 7, 2006), *available at* http://newsroom.ucla.edu/portal/ucla/PRN-UCLA-Study-Finds-Same-Genes-Act-7177.aspx.

4. COMM. ON UNDERSTANDING THE BIOLOGY OF SEX AND GENDER DIFFERENCES, INST. MED., EXPLORING THE BIOLOGICAL CONTRIBUTIONS TO HUMAN HEALTH: DOES SEX MATTER? x (Theresa M. Wizemann and Mary-Lou Pardue eds., 2001).

picture of who we are, and the possibility of changing who we are, in profound and new ways at a molecular level. It's my hypothesis that evolution is no longer natural selection as the Darwinian school ultimately pronounced it. With the advent of genetic engineering, we can and are changing the very nature of created life. And that's not an exaggeration. And it's only really been possible for the last decade. It's a new time in our history. Imagine these things: human cloning, engineering the characteristics of new humans being prepared, as DARPA is trying to do, for specific functions like war, where pain or the awareness of pain is muted, where bleeding can be stopped virtually instantly by an individual. We are learning to prolong the lifespan more and more, perhaps some people think indefinitely. We are creating new biological systems capable of reproduction and, if this is so, also capable themselves of evolution.

So these questions come up now, which of course wouldn't have been imagined when I was even an associate professor, much less a medical student. Will it be an advantage as we create these new life forms to retain two sexes? Interesting question. If we eliminate biological sex in our new forms of life before we understand the nature and extent of biological sex expression on genes, what will be the consequence to form and function of the finished product? We don't know. So does the study of the impact of sex, biological sex, on gene expression deserve more attention? And if you read the genomic literature, there is very little reference to male or female. It's just a paean, if you will, of praise and interest in the molecular biology of genetics, but it does not take gender or sex at all, that I have seen in any case.

What scientists should be, and are, worrying about is: the economics of what we're doing, the nature, and number of living beings, and the redistribution of power as a result of what we are doing, both planned and unplanned. We are changing the rate and mechanisms of evolution of living things profoundly. If there is a choice between preserving the earth in a viable state, or continuing the human race, we will probably opt to continue the race. This quote, I think, is very good: "[I]f the molecular, cellular, and genetic machinery used to conceive, develop, and operate a human were designed rather than the result of evolution, humans would be different and life would look different."[5]

Now we have this new discipline of synthetic biology, which is the ability to create living organisms from inert chemicals. Venter's group in May 2010 reported the design, synthesis and assembly of a genome from inert chemicals and its transplantation into a recipient's cell to create new

5. S. Jay Olshansky et al., *What if Humans Were Designed To Last?*, THE SCIENTIST, March 1, 2007, at 28.

cells which were controlled only by the synthetic chromosome.[6] This brought forth, as you can imagine, a whole welter of opinions. President Obama, predictably, formed a counsel, a Commission for the Study of Bioethical Issues, to focus on this kind of research. George Church said, in effect, that this was not so wonderful an achievement as advertised. As he said, "printing out a copy of an ancient text is not the same as understanding the language."[7] So he is an archconservative. But there were theologians and ethicists who said that this challenged our very concept of whether or not life had a spiritual side at all, and in some instances, whether God existed, and whether man had free will.

We are at a different time, I must say, in science. Sir John Maddox, the former editor of *Nature*, said:

> My guess is that if the question of human extinction is ever posed clearly, people will say that it's all very well to say we've been a part of nature up until now, but at this turning point in the human race's history, it is surely essential that we do something about it; that we fix the genome, to get rid of the disease that's causing the instability, if necessary we clone people known to be free of risk because that's the only way in which we can keep the human race alive. A still, small voice may at that stage ask what right does the human race have to claim precedence for itself. To which my guess is the full-throated answer would be, sorry, the human race has taken a decision, and that decision is to survive. And, if you like, the hell with the rest of the ecosystem.[8]

That's a provocative and interesting comment. Another pair of experts say this: "Given the momentum and the international character of research in synthetic biology, it is already too late to impose a moratorium, if indeed one were ever contemplated."[9] I'm reminded of the legend of Prometheus who gave men fire and the gods, as you know, chained him to a rock. His liver was eaten out by raven in punishment, restored at night and he was exposed to the same ordeal the next day. So we are, perhaps, a little like Prometheus.

I think we should be focusing a gender specific lens on men. It's all been about women's health and our excitement about this, we've sort of caught up on that both emotionally and intellectually. We have to continue

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6. Daniel G. Gibson et al., *Creation of a Bacterial Cell Controlled by a Chemically Synthesized Genome*, SCIENCE, July 2010, at 52.

7. George Church, Opinion, *Life After the Synthetic Cell: Now Let's Lower Costs*, 465 NATURE 422, 422 (2010).

8. *Complexity and Catastrophe: A Talk with Sir John Maddox*, EDGE, http://edge.org/conversation/complexity-and-catastrophe (last visited Oct. 26, 2011).

9. Jonathan B. Tucker & Raymond A. Zilinskas, *The Promise and Perils of Synthetic Biology*, NEW ATLANTIS: J. TECH. & SOC'Y, Spring 2006, at 25, 44.

of course to pursue information about women but we should also focus that same kind of gender-specific lens on men. Why do men die first? Why does coronary disease have its symptoms in the thirties in many men, and why do men with established coronary disease usually die at or about the age of sixty-five? That's just not acceptable. I think instead of going red for women we should also go blue for men in the American Heart Association. And look at some of these sex-specific vulnerabilities of males, who have been so generous, I have to say, in agreeing to be the exclusive subjects of our research for these many decades. I think it's extremely important. Florence Haseltine and I both testified at the Institute of Medicine to this expert committee who said, "Is gender-specific medicine important?" I said then, and I'm saying again: it remains to be seen whether or not what we are finding out about the sex-specific unique characteristics of each gender, when applied, actually improve survival and help us prevent and cure disease. We have been generating a tremendous amount of information, and it is now important to translate that into whether or not in fact it does help protect and preserve human life.

On a final note, one reason why I agreed to come to this meeting is because I have long wanted to have a colloquium between jurists, lawyers, theologians, anthropologists, historians, and scientists about the legal and moral implications of the new science, both of genomic science and, more specifically, of synthetic biology. So thank you for inviting me, it has been a wonderful morning, and I'm sure the afternoon will be just as rich.

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